Anti-Fentanyl Monoclonal Antibodies: In Vitro Characterization and In Vivo Efficacy in Reversing Apnea in Pigs

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The incidence of fatal drug overdose has increased dramatically due to the proliferation and widespread availability of fentanyl and its analogs, surpassing 100,000 in 2021 during the COVID-19 pandemic. Monoclonal antibody (mAb)-based therapeutics for opioid use disorder and overdose are in development; however, several key questions remain to be addressed relating to their safety and efficacy. Anti-fentanyl mAb have been proposed to reverse fentanyl overdose by binding fentanyl in circulation, causing fentanyl to redistribute out of brain and other organ tissue and reducing concentration of fentanyl available to activate opioid receptors. While efficacy of mAb in both prevention and reversal of fentanyl respiratory effects by mAb has been shown in rodent models, further evidence of efficacy in large animal models is required to support translation. Here, we sought to evaluate efficacy of a lead anti-fentanyl mAb in a pig model of fentanyl-induced apnea, and to assess the potential for side effects of mAb. We found that anti-fentanyl mAb did not reduce efficacy of off-target anesthetics (including propofol, droperidol and ketamine) in rats, and that mAb-bound fentanyl was unable to activate mu opioid receptors in vitro. To predict the effect of mAb on fentanyl metabolism, rat liver microsomes were incubated in vitro with fentanyl with or without an excess of mAb, and the relative rate of metabolism was determined. Finally, to evaluate efficacy of mAb in reversing fentanyl-induced apnea in pigs, Hanford miniature swine were anesthetized with isoflurane, and given an infusion of fentanyl until 2 minutes of continuous apnea occurred. Then, fentanyl infusion was discontinued, and either naloxone or the lead anti-fentanyl mAb was administered i.v. Respiratory parameters were monitored at 1-minute intervals until recovery. Whereas control subjects returned to spontaneous breathing in approximately 7-8 min, naloxone-treated subjects recovered within 1 min and mAb-treated subjects within 2 min. Concentration of fentanyl in serum was determined after apnea and during reversal, which showed that treatment with mAb increased serum fentanyl 10-20-fold within the first minute after infusion. These results support further development of anti-fentanyl mAb as a possible treatment for fentanyl overdose.

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